Pregabalin (LYRICA) C-V
Criteria for Use
June 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information. For additional information, refer to the references cited at the conclusion of this document.

Transitioning Veteran *Pregabalin is on the DoD VHA Transitional Continuity of Care Drug List; if the criterion is met, the remainder of the criteria for use is not applicable.*

☐ Veteran is transitioning care from the Department of Defense to VHA. A VA prescriber, after assessing and consulting with the Veteran, has determined that continuation of pregabalin is safe and clinically appropriate.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive pregabalin.*

☐ Hypersensitivity to pregabalin or product components.

☐ Use of pregabalin for chronic low back pain or chronic pain due to osteoarthritis of the hip or other joints

☐ Use of pregabalin for panic disorder, obsessive compulsive disorder, post-traumatic stress disorder or alcohol use disorder

☐ Use of pregabalin for acute perioperative pain or for the prevention of chronic postoperative pain (see *Issues for Consideration*)

☐ History of gabapentinoid abuse (see *Issues for Consideration*)

☐ Use of pregabalin in combination with gabapentin.

Inclusion Criteria *The answers to one of the following (A–G) must be fulfilled in order to meet criteria.*

See "Issues for Consideration" for definition of adequate trial duration, information on gabapentin dosing, comparison to other medications, and safety information

A. Patient has **Painful Diabetic Neuropathy** AND has a well documented intolerance or insufficient response to gabapentin AND at least one oral agent, used alone or in combination, from 1 of the 4 drug classes shown below (minimum total of 2 agents trialed including gabapentin)

- ☐ 1) Tricyclic antidepressants (TCAs): amitriptyline (nortriptyline) 25–150 mg/d; desipramine 12.5–200 mg/d; or imipramine 25–225 mg/d
- ☐ 2) Serotonin-norepinephrine reuptake inhibitors (SNRIs): venlafaxine 37.5mg start dose; titrate to 150–225 mg/d; duloxetine 60 mg/d
- ☐ 3) Antiepileptic drug (AED): valproate 500–1250 mg/d
  Only applies to patients who may already have had a trial of valproate; a new trial of this agent is neither required nor recommended.
- ☐ 4) Opioid: *The criteria do not recommend or require a prior trial of a schedule II to IV opioid before considering pregabalin; a previous trial of opioid may be counted towards the number of trials required before consideration of pregabalin.*

Note: Topical capsaicin 0.075%; applied 3 to 4 times daily ≥ 4 weeks is also a reasonable option.

B. Patient has **Postherpetic Neuralgia**, requires systemic therapy, AND has a well documented intolerance or insufficient response despite an adequate trial of gabapentin (*Note: Duloxetine or a TCA are also reasonable options; doses above)*

Patient has **Localized Postherpetic Neuralgia** and has a well documented intolerance or insufficient response despite a prior adequate trial of gabapentin and one of the topical agents below:

- ☐ 1) Topical capsaicin 0.075%: apply 3 to 4 times daily
- ☐ 2) Lidocaine patch 5%: apply up to 3 patches, only once for up to 12 h, within a 24-h period.

C. Patient has **Partial-onset Seizure Disorder**, is concurrently treated with at least one other antiepileptic drug, and has a well documented intolerance, hypersensitivity, contraindication, or insufficient response despite an adequate trial at maximally tolerated doses of at least 3 of the agents listed below (trial duration dependent upon baseline seizure rate):

- ☐ Carbamazepine, gabapentin, lamotrigine, levetiracetam, phenytoin, topiramate, valproate

D. Patient has a documented diagnosis of **Fibromyalgia** and meets all of the following criteria:

- ☐ Has fibromyalgia symptoms characterized as moderate to severe
- ☐ Has had a previous or concurrent trial of at least one guideline-concordant nonpharmacologic treatment effective in the management of fibromyalgia (e.g., graded exercise program, cognitive behavioral therapy)
- ☐ Has a well documented intolerance, contraindication or insufficient response to a TCA (see list of agents and doses above)
- ☐ Has a well documented intolerance, contraindication or insufficient response to a serotonin-norepinephrine reuptake inhibitor (SNRI): duloxetine (30-120 mg/d) or milnacipran (100-200 mg/d)

Note: Gabapentin or a selective serotonin-reuptake inhibitor (SSRI): fluoxetine (10 to 80 mg/d), sertraline (50 to 200 mg/d), paroxetine (20 mg/d start dose, max of 60 mg/d) are also reasonable options

*Consider the use of TCA, SSRI, or SNRI antidepressants for management of patients with fibromyalgia and concurrent fatigue or depression and consider use of a gabapentinoid in patients with comorbid anxiety or sleep interference. Combined use of antidepressant agents with pregabalin (or gabapentin) may result in additive central nervous system depressant effects [*see *Issues for Consideration].*

E. Patient has a documented diagnosis of **Neuropathic Pain associated with Spinal Cord Injury** and has a well documented intolerance, contraindication or insufficient response despite adequate, separate trials of a TCA **AND**:

☐ Gabapentin (consider for patients with comorbid anxiety or sleep issues)

OR

☐ Duloxetine (start dose 30 mg/d, increase to 60 mg/d as tolerated)

Consider gabapentin for patients with comorbid anxiety or sleep interference; consider duloxetine for patients with comorbid depression or fatigue.

F. Patient has a documented diagnosis of **Restless Legs Syndrome** and has a well documented intolerance or insufficient response to gabapentin (initial dose 100 to 300 mg 2 hours before bedtime; usual effective dose 900 to 2400 mg/d in two divided doses) AND an adequate trial of at least one dopamine agonist oral agent:

☐ 1) Pramipexole (initial daily dose 0.125mg; maximum daily dose 0.5 to 1.0mg)

☐ 2) Ropinirole (initial daily 0.25 to 0.5mg; maximum daily dose 4mg)

G. Patient has a documented diagnosis of **Generalized Anxiety Disorder (GAD) or Social Anxiety Disorder (SAD)** and has a well-documented intolerance or insufficient response to one agent from each drug class below:

☐ 1) Selective serotonin-reuptake inhibitors (SSRI): escitalopram (10 mg/d start dose, max dose 20 mg/d); sertraline (50 mg/d start dose, max of 200 mg/d); paroxetine (20 mg/d start dose, max of 60 mg/d);

☐ 2) Serotonin-norepinephrine reuptake inhibitor (SNRI): venlafaxine (37.5 mg/d start dose, max up to 225 mg/d).

Pregabalin may be used as monotherapy (after SSRI and/or SNRI as specified above) or second-line as add-on to previous SSRI or SNRI regimen.

Discontinuation Criterion

No benefit after at least 12 weeks of treatment at maximally tolerated doses of pregabalin.

Increased seizure frequency may occur in patients with seizure disorders if pregabalin is rapidly discontinued; gradual withdrawal of therapy is recommended.

Refills

Maximum 2 refills allowed on initial 30 day prescription; tolerance to, and continuation of, pregabalin should be re-evaluated after 12 weeks of therapy

Pregabalin Dosing in normal renal function (CrCl ≥ 60 ml/min)

Indication	**Painful diabetic neuropathy**	**- Postherpetic neuralgia - Partial-onset seizures - Neuropathic pain associated with SCI - GAD/SAD**	**Fibromyalgia**	**Restless Leg Syndrome**
Initial daily dose	50 mg 3 times daily or 75mg 2 times daily [28] (150 mg/d)	75 mg 2 times daily or 50 mg 3 times daily (150 mg/d)	75 mg 2 times daily (150 mg/d)	50 to 75 mg 1 to 3 hours before bedtime
Maximum daily dose	300 mg/d	600 mg/d	450 mg/d	150 to 450 mg 1 to 3 hours before bedtime

Consult appropriate references for dosing in patients with renal impairment including those receiving hemodialysis.

Issues for consideration

- Administration of pregabalin for acute postoperative pain has been shown to have additive analgesic effects and an opioid-sparing effect; however, use can also be associated with increased side effects (sedation, somnolence, dizziness, visual disturbances) and potentiation of opioid-induced cognitive impairment and respiratory depression.[1-5]
- There is inadequate evidence to support the use of pregabalin for the prevention of chronic postoperative pain.[1, 6, 7]
- Pregabalin has euphorigenic activity particularly when combined with opioids and alcohol; patients with a history of substance use disorder (particularly those with history of opioid use disorder) are at high risk for abuse of pregabalin.[8]
- Duration of medication trials should be ≥ 6 weeks unless otherwise noted.
- In a recent systematic review and meta-analysis of trials of pharmacotherapy for neuropathic pain, TCAs were found to have a lower overall NNT compared to other oral agents. While TCAs should be considered in appropriate candidates, tertiary amine TCAs (amitriptyline and imipramine) are not recommended at doses greater than 75 mg/day in adults aged 65 years and older because of major anticholinergic and sedative side-effects and potential risk of falls. In addition, an increased risk of sudden cardiac death has been reported with TCAs at doses greater than 100 mg daily.[9]
- Except as noted, dosing of gabapentin constituting an adequate trial: 1) maximum tolerated dose OR 2) dose ≥ 1800 mg/d in patients with CrCl ≥ 60 mL/min (see appropriate reference for dosing in renal impairment).
  Tolerance of gabapentin is maximized when treatment is started at a low daily dose (100-300mg HS) followed by slow up titration every few days until clinical benefit is obtained or a maximum dose of 3600 mg/d is reached (max dose in normal renal function; see appropriate reference for dosing in renal impairment).

- Consensus recommendations for painful diabetic neuropathy: *American Academy of Neurology (2011):* Level A: pregabalin; Level B: gabapentin, sodium valproate, amitriptyline, SNRIs, topical capsaicin, opioids; Level C: lidocaine patch*; European Federation of Neurological Societies Task Force (2010):* 1st line: Gabapentinoids, TCAs, SNRIs; 2nd line: tramadol with/without acetaminophen, opioids.[10, 11,]
- Consensus recommendations for postherpetic neuralgia: *American Academy of Neurology (2004) and European Federation of Neurological Societies Task Force (2010)* both list gabapentinoids, TCAs and lidocaine patch as 1st line; Canadian Pain Society (2014): 1st line gabapentinoids, TCAs, and SNRIs.[11, 12, 13]
- Treatment of fibromyalgia with medications alone is typically unsuccessful. All patients should receive education about the nature of the disorder and counseling regarding the role of exercise and cognitive behavioral techniques.
- Pharmacological therapy for fibromyalgia should be guided by the predominant symptoms that accompany pain; all patients should trial a low-dose tricyclic antidepressant unless a contraindication or previous intolerance exists.
- Dopamine agonists are preferred over gabapentinoids in patients with restless leg syndrome (RLS) who have very severe RLS, comorbid depression or dysthymia, or obesity/metabolic syndrome; alternatively, gabapentinoids are preferred when there is comorbid pain from other source, anxiety, sleep interference, impulse control disorder or addiction (in patients with addiction, gabapentin is preferred over pregabalin due to potential abuse of pregabalin in these patients).
- Treatment of RLS with pregabalin 300mg did not result in superior results compared to pramipexole 0.5mg daily. There is less augmentation (worsening over time) of RLS symptoms with pregabalin compared to pramepexole, as well as lower rates of nausea, vomiting and headache; however, pregabalin is associated with higher rates of suicidal ideation, dizziness, somnolence, and weight gain compared to pramipexole.[25]
- Pregabalin has been designated Pregnancy Category C; however, a recent multicenter prospective study indicated that first trimester exposure to pregabalin was associated with a higher risk for major birth defects.[29] If inadvertent exposure occurs during pregnancy, close monitoring of the mother and fetus/newborn is recommended. A registry is available for women exposed to pregabalin during pregnancy (www.aedpregnancyregistry.org).
- Antiepileptic drugs, including pregabalin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication.
- Pregabalin treatment may cause peripheral edema or weight gain. US prescibing information indicates the incidence of weight gain with pregabalin (up to 16%) is greater than that associated with gabapentin (up to 3%).

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